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Review

Endocrine-disrupting metabolites of alkylphenol ethoxylates – A critical review of analytical methods, environmental occurrences, toxicity, and regulation

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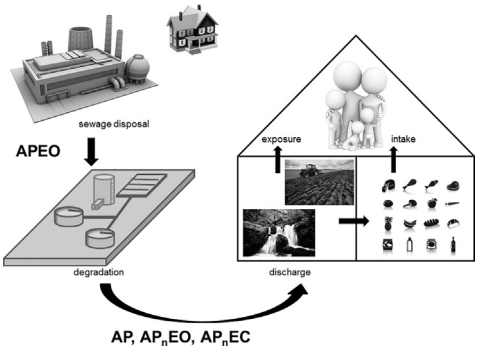
HIGHLIGHTS

- Comprehensive, authoritative, critical, and readable review of alkylphenol ethoxylate (APEO) metabolites
- Collection of analytical methods, environmental occurrences, toxicity and regulation of endocrine disruptors
- Highlights the effect of APEO metabolites on immune and nervous system
- Underlining information gaps and further research directions

GRAPHICAL ABSTRACT



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ABSTRACT

Despite the fact that metabolites of alkylphenol ethoxylates (APEO) are classified as hazardous substances, they continue to be released into the environment from a variety of sources and are not usually monitored. Their wide use has led to an increase in the possible exposure pathways for humans, which is cause for alarm. Moreover, there is a lack of knowledge about the behaviour of these metabolites with respect to the environment and toxicity, and their biological effects on human health. The aim of this work is to give an overview of the APEO metabolites and their analysis, occurrences and toxicity in various environmental and human samples. APEO metabolites have adverse effects on humans, wildlife, and the environment through their release into the environment. Currently, there are some reviews available on the behaviour of alkylphenols in soil, sediments, groundwater, surface water and food. However, none of these articles consider their toxicity in humans and especially their effect on the nervous and immune system. This work summarises the environmental occurrences of metabolites of APEOs in matrices, e.g. water, food and biological matrices, their effect on the immune and nervous systems, and isomer-specific issues. With that emphasis we are able to cover most common occurrences of human exposure, whether direct or indirect.

Contents

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1. Introduction

One of the major groups of nonionic surfactants are 4-alkylphenol ethoxylates (APEOs), e.g. nonylphenol and octylphenol ethoxylates (Raecker et al., 2011; White, 1994; Ying et al., 2002). The ability to concentrate at different surfaces and form micelles in solutions is the main characteristic of surface-active compounds. The amphiphilic structure of the surfactant molecule, which has a polar (hydrophilic) and nonpolar (hydrophobic) part, is the reason for their surface activity. The hydrophilic character of APEOs is due to a polyethoxylate chain with ethoxylate units from 1 to 40. The opposite hydrophobic property is provided by alkylphenols with branched hydrocarbon chains containing eight, nine or twelve carbon atoms (Thiele et al., 1997). The most common APEOs are octylphenol ethoxylates (OPEO), nonylphenol ethoxylates (NPEO) and dodecylphenol ethoxylates (DOEO) (White, 1994).

Because APEOs are surfactants, they are widely used for cleaning formulations and as industrial process aids. They therefore have a broad range of applications, including as dispersing agents in paper and pulp production, emulsifying agents in latex paints and pesticide formulations, flotation agents, industrial cleaners (metal surfaces, textile processing and the food industry), cold cleaners for cars, and household cleaners (Thiele et al., 1997). Most APEOs are used in aqueous solutions for ease of handling, which means that they are discharged into municipal and industrial wastewaters and then transported to sewage treatment plants. During the different stages of sewage treatment, APEOs undergo a complex biodegradation process in which several microorganisms metabolise the APEOs by their ethoxy chain and form several degradation products, including 4-alkylphenols (AP), (4-alkylphenoxy) acetic acid (AP1EC), (4-alkylphenoxy) ethoxy acetic acid (AP2EC), 4-alkylphenol monoethoxylate (AP1EO), and 4-alkylphenol diethoxylate (AP2EO) (Fig. 1). These degradation products are persistent, bioaccumulative and toxic. Some are already considered priority substances (e.g. octylphenol [OP]) or listed as priority hazardous substances in the Water Framework Directive of the European Union (e.g. nonylphenol [NP]). Of these substances, NP (La Guardia et al., 2001) is considered to be the most significant and dangerous metabolite; the most common NPs and OPs are shown in Fig. 2.

Various APEO metabolites are ubiquitous in many environmentally relevant matrices (e.g. influent and effluent water from sewage treatment plants, river water, marine water, surface water, groundwater, drinking water, sediments and soil) (Ying et al., 2002; Thiele et al., 1997; La Guardia et al., 2001; Loos et al., 2008; Loos et al., 2007; Soares et al., 2008; Zhong et al., 2017a), including food (Raecker et al., 2011; Guenther et al., 2002; Dodder et al., 2014; Günther et al., 2017; Hao et al., 2018), drinking water (Maggioni et al., 2013; Fan et al., 2013; Van Zijl et al., 2017; Lee et al., 2017a) and human tissue samples (Ferrara et al., 2011; Chen et al., 2016; Park and Kim, 2017), and are even more toxic than their parent compounds (Ahel et al., 1994; Scott and Jones, 2000). Besides the negative properties mentioned, some metabolites such as NPs can act like the female hormone 17β-estradiol by binding to the estrogen receptor and displacing 17β-estradiol in a competitive manner (White, 1994; Soto et al., 1991).

Since estrogenic effect and degradation behaviour in the environment of individual APEOs and their metabolites are heavily dependent on the structure and bulkiness of the side chain, it is absolutely necessary to consider this problem from an isomer-specific viewpoint. Studies have shown that the estrogenic potential of a single isomer is two to four times higher than the reference substance, and when comparing the easiest biodegradable isomers with the most persistent ones, the half-lives are three to four times longer. Single isomers of APEO metabolites are important for assessing their ecological and health effects. This holds true even for their enantiomers since biological systems are enantioselective (Gabriel et al., 2007; Gabriel et al., 2005a; Gabriel et al., 2005b; Gabriel et al., 2008).

An alarming consequence of the wide use and diffusion of APEOs into the environment through diverse sources is the increase in the exposure pathways to their metabolites for humans and wildlife. These pathways include the ingestion of food and meat products that come from land that is contaminated or irrigated with contaminated water, and the consumption of tap water from polluted groundwater or surface water (Careghini et al., 2015; Weber et al., 2006; Molnar et al., 2013). However, the risk assessment and also important toxicological studies on these substances were established without consideration of isomer-specific effects.

For most metabolites, the effects on humans (especially with regard to the immune and nervous systems) and the environment have not been sufficiently investigated. Nevertheless, their effect on these systems (e.g. human and environment) could be significant, which is why APEO metabolites still play an important role in the debate (Siddique et al., 2016).

The outline of this review is as follows: The first sections are dedicated to the synthesis and analytical methods for APEOs and the determination of their metabolites. This is followed by a discussion of their occurrences and concentrations in environmental and biological matrices including human tissues. Next, an overview of their toxicity is given,

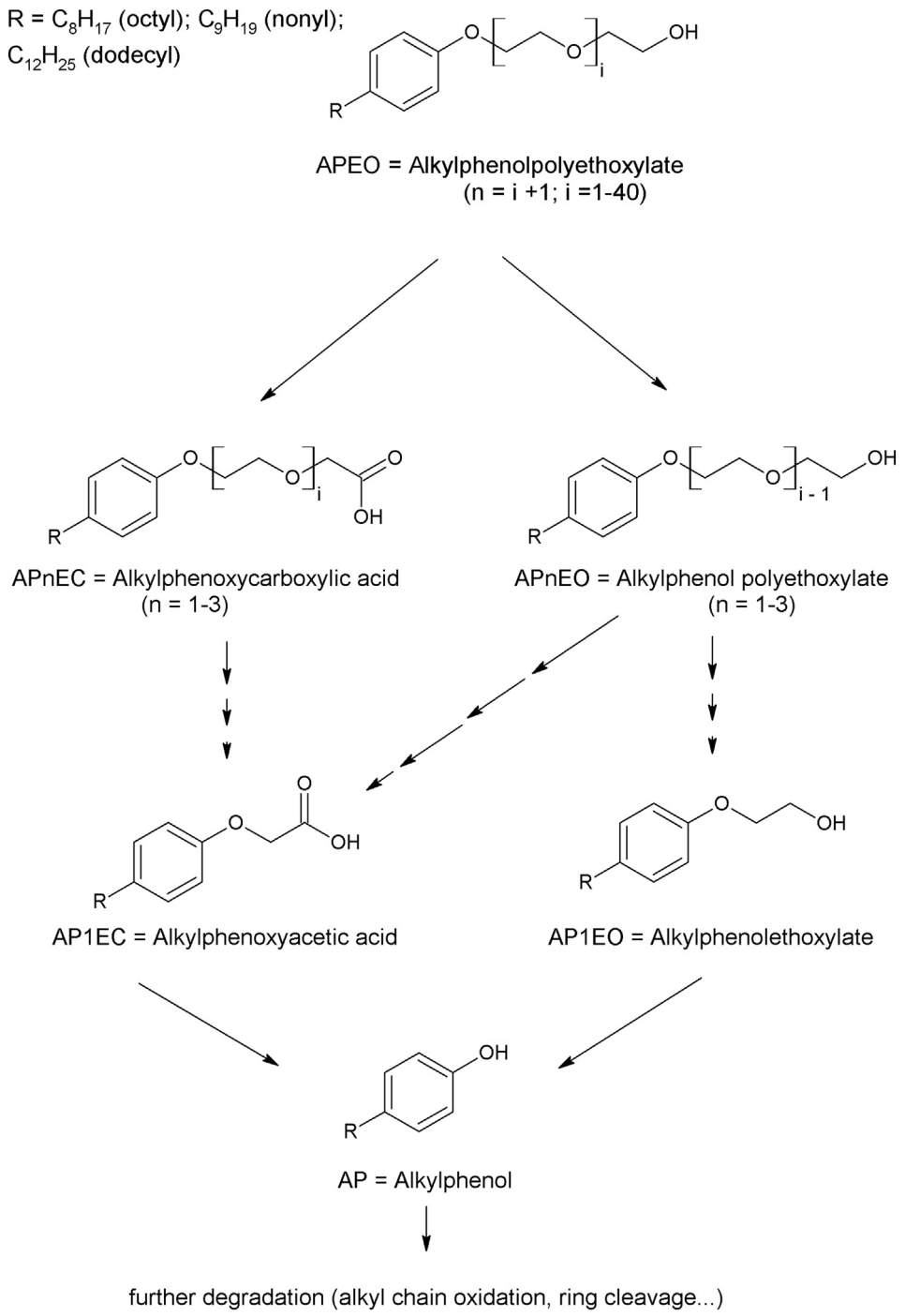

Fig. 1. Schematic degradation pathway of alkylphenolethoxylates and formation APEO metabolites.

including the effects on cognitive function and regulation. Finally, we emphasise the need for further research and summarise the tasks that are suggested by the data gathered here.

2. Production, applications and markets

The main compound for the synthesis of APEOs is phenol. Depending on the desired APEO, there are three possible routes for the synthesis of these nonionic surfactants. In an alkylation of phenol with trimethylpentene the product is 4-*tert*-octylphenol (OP), in an acid catalysed reaction with a nonene isomer mixture the product is a 4-nonylphenol (NP) mixture, and with a complex olefin feedstock with 70% C_{12}-alkyl content the product is a 4-dodecylphenol (DP) mixture. These are preproducts for the APEO synthesis. The synthesis of NP and DP already yields a complex mixture consisting of isomeric compounds with variously branched structures of their side chains. Alkylphenol ethoxylates are then synthesised via a reaction with ethylene oxide and potassium hydroxide/ethanol as the catalyst (Thiele et al., 1997; Priac et al., 2017). Finally, this results in a mixture of oligomer homologues with varying lengths of the polyethoxy chain.

With respect to nonionic surfactants, APEOs are major substances widely used as detergents, emulsifiers, wetting and dispersing agents,

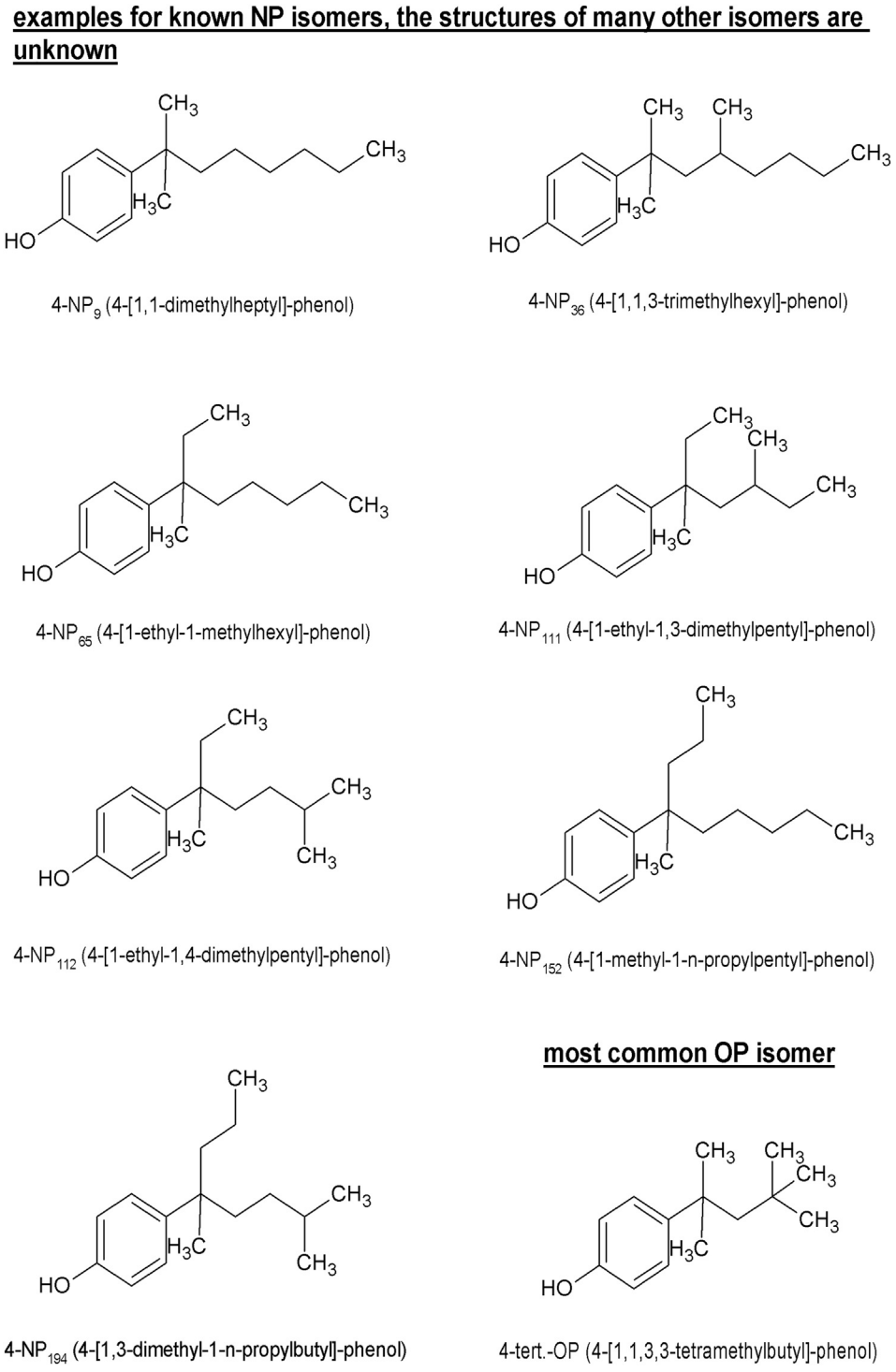

Fig. 2. Examples for NP isomers (IUPAC name and designation according to Juelich nomenclature (Guenther et al., 2005) and most common OP isomer).

antistatic agents, demulsifiers and solubilisers in domestic, agricultural and industrial products. The most widely used APEO is nonylphenol ethoxylate (NPEO), which accounts for 80 to 85% of all APEOs produced, with octylphenol and dodecylphenol ethoxylates (OPEO & DPEO) (United States Environmental Protection Agency, 2010) making up the rest. Annual worldwide consumption of APEOs in 2000 was about 700 kilotonnes (Zgoła-Grześkowiak et al., 2015). In a more recent study, the estimate for global consumption was 612 kilotonnes (Janshekar et al., 2010). With regard to NPEOs alone, their current emissions were calculated to be above 11 kilotonnes per year in the European Union (EU) (COHIBA Guidance Document No. 6, 2011) and around 160 kilotonnes in North America (United States Environmental Protection Agency, 2008). In looking at the total consumption of NP, OP, DP, OPEO and DPEO in the EU, their amounts were 25,000–50,000, 22,900, 50,000, 1000 and < 1000 t/y, respectively (Danisch Ministry of the Environment, 2013). In Western Europe, usage of APEOs has declined as a result of the self-regulation of European industry. On the other hand, consumption of APEOs is expected to rise in the growing Asian

market (Chiu et al., 2010). The statistics for NP in India show a growing market with an estimated annual NPEO consumption of between 40 and 44 kilotonnes (Dutta, 2008).

3. Analysis

3.1. Sampling, storage and extraction

Different kinds of sampling and storage procedures must be used, depending on the type of sample to be analysed. What is most important during sampling and storage is that no changes should take place during these procedures in order to get reliable analytical results. A major problem in the analysis of surfactants is their amphiphilic nature, giving them the ability to adsorb on various surface boundaries, which can lead to losses on these surfaces. To overcome this problem, it is necessary to add an internal standard to the sample and be able to correct for nonquantitative recovery during isolation and quantification.

In handling environmental samples, it is crucial to minimise and prevent microbial degradation of the surfactant immediately after collection. This is done with chemical biocides. The general procedure for water samples from sewage treatment plants, rivers or seas is to preserve them with 1% formaldehyde and store them at 4 °C in a glass bottle (Ahel et al., 1994; Ahel and Terzic, 2003). This procedure is sufficient to keep the samples stable for up to 4 weeks (Kubeck and Naylor, 1990). Not only diurnal but also seasonal variations of the APEO concentrations in influents and effluents of sewage treatment plants require automated, continuous sampling (Giger et al., 1987; Minarik et al., 2014; Motegi et al., 2007).

Sludge samples are processed in the same way as water samples, but without preservation (La Guardia et al., 2001). However, aluminium vessels can be substituted for the glass bottles (Jobst, 1995). Agricultural land treated with contaminated sewage sludge has to be monitored for APEOs and their metabolite concentrations in soil. Sampling and storage for soil is performed starting with collection of the plough layer (approximately the top 20–30 cm) of the soil sample, partial air-drying at room temperature, sieving to 2 mm and storing at −20 °C (Gibson et al., 2010).

Sampling and preserving biological samples is challenging with regard to the samples' representativeness and the ability to ensure that the composition of those samples remains unchanged during storage (Thiele et al., 1997). Nevertheless, the Environmental Specimen Bank (ESB) of Germany has developed several methods to overcome these challenges (Emons et al., 1997; Schladot et al., 1993). One method involves repeatedly collecting different specimen types from terrestrial and aquatic environments and freezing them immediately at a temperature of below −150 °C with liquid nitrogen right after sampling. Precrushing, grinding and homogenisation are carried out under the same cryogenic conditions before long-term storage.

A recently developed sample preparation method for biological matrices is the “quick, easy, cheap, effective, rugged, and safe” (QuEChERS) method, with over 80% absolute recoveries in GC–MS measurements for specific alkylphenols (Plassmann et al., 2015). The most common extraction and preconcentration method is solid phase extraction (SPE) (Sghaier et al., 2017; Omar et al., 2015; Bergé et al., 2012; Vallejo et al., 2011). Usually SPE consists of three steps: conditioning, application of the sample with the potential inclusion of a washing step, and finally the elution of the analyst. Depending on the sample the conditioning of the SPE is with organic solvent and purified water. After the application of the sample the washing step is again with purified water. The analytes on the SPE cartridge are eluted with organic solvent (Vega-Morales et al., 2010). For further information on preconcentration of alkylphenol metabolites we refer to Table 1 and the references therein. Another extraction method is stir bar sorptive extraction (SBSE) with recoveries of 83–118% (Cacho et al., 2012).

3.2. Analytical methods for determination of APEOs

Gas chromatographic (GC) and liquid chromatographic (LC) analysis are the most widely used chromatographic systems for the determination of APEOs. Often, these systems are coupled to mass spectrometric systems which are sensitive and specific, such as single or triple quadrupole mass spectrometer (QMS) or time-of-flight mass spectrometer (TOF-MS), and used to identify the structure of APEO metabolites (Lu and Gan, 2014a; Thiele et al., 2004; Moeder et al., 2006).

Generally, GC–MS is a suitable method for the analysis of alkylphenolic compounds because less volatile compounds can be converted into more volatile products (Sghaier et al., 2017) using a derivatization step. Actually, the derivatisation step is not necessary for the APEO metabolites (Eganhouse et al., 2009) because it could lead to a loss of analyte. On the other hand, this step allows for the discrimination of matrix compounds and thus leads to increased sensitivity. Nevertheless, GC–MS analysis is an easy and fast method for the determination of APEOs, which is shown by different groups (Sghaier et al., 2017; Omar et al., 2015; Vallejo et al., 2011; Lu and Gan, 2014a; Eganhouse et al., 2009; Wu et al., 2013; Durán-Alvarez et al., 2009; Meador et al., 2016; Wu et al., 2010; Katase et al., 2008; Gibson et al., 2007).

For some samples it is not feasible to perform a GC–MS analysis. In that case, it is necessary to carry out an LC-MS analysis (Loos et al., 2007; Ahel et al., 1994; Vega-Morales et al., 2010; Datta et al., 2002; Rice et al., 2003; Loyo-Rosales et al., 2007). A more sensitive and solvent-poor technique is ultra-performance liquid chromatography coupled with tandem mass spectrometry (UPLC-MS/MS) (Lara-Martín et al., 2012). Another recent LC-MS technique uses a dual column system for an online preconcentration of endocrine disruptor compounds (EDC) and an improvement of total analysis time (Gorga et al., 2014). A brief overview of the different methods used for APEO metabolite determination is given in Table 1. Besides sample analysis with LC-MS, this technique can be used for the fractionation of technical alkylphenols for further analysis (Gundersen, 2001; Günther et al., 2001), e.g. assays (Kim et al., 2004; Kim et al., 2005).

Before the widespread use of mass spectrometer detectors, Fourier transform infrared spectroscopy (FTIR) was used for confirmation of the *para* substitution (Wheeler et al., 1997). With this method, structural elucidation of synthesised APEO metabolites are confirmed by ^{1}H or ^{13}C nuclear magnetic resonance spectroscopy (NMR) (Thiele et al., 2004; Boehme et al., 2010; Ruß et al., 2005; Uchiyama et al., 2008). Another special technique with less sensitivity is capillary electrophoresis (CE) (Mori et al., 2001; Regan et al., 2002; Katayama et al., 2003).

3.3. Isomer and enantiomer-specific determination

Since we already knew that the production of APEOs, and especially of NPEOs and DOEOs, results in a complex mixture because of the precursors, the problem is not a single compound issue. Due to the various branching and length on the side chain of the phenol ring, a mixture could include >100 isomers and congeners, e.g. technical nonylphenol (tNP) (Eganhouse et al., 2009; Ieda et al., 2005). Different groups have analysed the tNP, however, they have only been able to identify a maximum of 18 isomers in the mixture (Gabriel et al., 2008; Vallejo et al., 2011; Lu and Gan, 2014a; Thiele et al., 2004; Moeder et al., 2006; Wu et al., 2013; Lu and Gan, 2014b; Wheeler et al., 1997). All these analyses were performed on either GC-FID, GC–MS or GCxGC–MS systems. The tNP, which consists of 90% 4-NP already has 211 possible constitutional isomers and this number increases to 550 if stereoisomerism is considered (Guenther et al., 2005). Efforts have been made to synthesise all the different isomers for NP isomers (Boehme et al., 2010). To our knowledge, however, the information for the others is lacking. In addition, this information is necessary for all the other APEO metabolites. Single isomers of APEO metabolites are important in terms of their ecological and health effects. This includes their enantiomers because biological systems are enantioselective. To date, few systematic analyses

Table 1
Exemplary analytical investigations on different APEO metabolites

compound	sample type	enrichment	column	detection	reference
NP, NPEO	sewage effluents	SPE	amino-silica columns	LC-MS	Ahel et al. 2000
OP,OPEO, NP, NPEO	fish sample	ASE + SPE	Hypersil APS normal phase column (4.6 mm i.d. × 100 mm, 5 μm particle size), flow: 1.1 mL	LC-Fluorescence	Datta et al. 2002
OP,OPEO, NP, NPEO	water sample	ASE + SPE	DB-17MS (30 m × 0.25 mm, 0.25 μm)	GC-MS	Rice et al. 2003
OP,OPEO, NP, NPEO	sediment, fish		MSpak GF-310 4D column (4.6 mm i.d. × 150 mm); flow: 0.2 mL	LC-MS/MS	Rice et al. 2003
OP,OPEO, NP, NPEO	water, sediment	ASE + SPE	MSpak GF-310 4D column, 4.6 mm i.d. × 150 mm; flow: 0.2 mL	LC-MS/MS	Loyo-Rosales et al. 2003
NP	water, suspended particles, sediments	SPE	Waters Amino column (μBondapak 3.9 mm i. d. x 300 mm x 5 μm)	LC-Fluorescence	Xu et al. 2006
NP	technical mixture	SPE	30 m HP5-MS (30 m × 0.25 mm, 0.25 μm)	GC-MS	Gibson et al. 2007
OP, OPEO, OPEC, NP, NPEO, NPEC	surface water	SPE	1) Synergi Polar-RP (150 x 2 mm, 4 μm particles); 2) Superspher 100 RP-18 (250 x 2 mm, 4 μm particles) flow: 1) 0.25 mL/min; 2) 0.4 mL/min	LC-MS/MS	Loos et al 2007
OPEO, OPEC, NPEO, NPEC	water, sediment, suspended particulate matter	SPE	MSpak GF-310 4D column (150 x 4.6 mm)	LC-MS/MS	Loyo-Rosales et al. 2007
NP	technical mixture	none	HP-5 (30 m × 0.25 mm, 0.25 μm)	GC-MS	Katase et al. 2008
NP	soil	ASE + SPE	HP5-MS fused silica capillary column (30 m × 0.25 mm, 0.25 m film thickness)	GC-MS	Duran-Alvarez et al. 2009
NP	technical mixture	none	Primary: DB-5 MS (30 m × 0.25 mm, 1.0 μm) Secondary: Supelcowax 10 (2.0 m × 0.1 mm, 0.1 μm)	GCxGC-TOFMS	Eganhouse et al. 2009
NP	technical mixture	none	BPX5 (30 m × 0.25 mm, 0.25 μm)	GC-MS	Wu et al. 2010
OP , OPEO, NP, NPEO	sewage samples	SPE	Pursuit XRs Ultra-C18 reversed phase column (2.8 m particle size, 50 mm × 2 mm i.d.)	LC-MS/MS	Vega-Morales et al. 2010
OP,OPEO, OPEC, NP, NPEO, NPEC	river water	ASE + SPE	GC-MS: DB-17MS (30 m × 0.25 mm, 0.25 μm) LC-MS/MS & Fluorescence: MSpak GF-310 4D column (150 x 4.6 mm)	GC-MS & LC-Flourescence&MS/MS	Loyo-Rosales et al. 2010
OP, NP	technical mixture	none	Primary :HP-5 MS (30 m × 0.25 mm, 0.25 μm) Secondary: DB-17MS (5 m × 0.25 mm, 0.25 μm)	GCxGC-MS	Vallejo et al. 2011
NP, NPEO, NPEC	sediment	Ultra sonic + SPE	Purospher STAR RP-18 (50×2 mm, 1.8 μm particle size) UHPLC column; flow: 0.4 mL/min	UPLC-MS/MS	Lara-Martin et al. 2012
OP & NP	surface water & sediments, suspended solids	liquid-liquid extraction + SPE	DB-5 MS (30 m × 0.25 mm, 0.25 μm)	GC-MS	Wu et al. 2013
NP	isomers	none	DB-5 UI (60 m × 0.25 mm, 0.25 μm)	GC-MS	Lu and Gan 2014
OP, NP, DP	technical mixture	none	Primary: HP5-MS (30 m × 0.25 mm, 0.25 μm) capillary column Secondary: DB-17MS (5 m × 0.25 mm, 0.25 μm) capillary column	GCxGC-qMS	Omar et al. 2015
NP	water & tissue		external laboratory	LC-MS/MS	Meador et al. 2016
NP	spiked matrix & river waters	SPE	Phenomenex XLB (60 m x 0.25 mm, 0.25 μm)	GC-MS	Sghaier et al. 2017

of enantiomers have been performed (Zhang et al., 2007; Acir et al., 2016; Zhang et al., 2009a; Zhang et al., 2009b). There is therefore a need for further research in this field.

4. Environmental occurrences

Occurrences of APEOs and their metabolites in the environment are due to anthropogenic activities. In-depth analyses of samples from different environmental compartments were done with respect to APEOs and their metabolites because they show very low biodegradability in sediments and are able to persist for decades (Lara-Martín et al., 2012). Consequently, our knowledge of the fate of APEOs in environmental matrices is good. There have been a couple of recent reviews which recap the problem of alkylphenols; however they are limited to NPs (Soares et al., 2008; Careghini et al., 2015), sediments and water (Ying et al., 2002; Priac et al., 2017; Ying, 2006) or have little information about APEO metabolites (Jardak et al., 2016). A more specific review of nonylphenol isomers was recently published by Lu and Gan (Lu and Gan, 2014b). All of the publications cited in these reviews will be dealt with briefly and supplemented with broader information about other metabolites. For an analytical overview of different biological matrices, please refer to Table 2.

4.1. Water and food

During the process of APEO-contaminated wastewater treatment, all the above-mentioned metabolites are formed and released into the aquatic environment. This treated water ends up as surface water or groundwater, which is then used as drinking water.

In the 90s, Ahel et al. detected metabolites of APEOs in groundwater from different field sites near Zagreb, Croatia with concentrations of <0.1 μg/L for NP, NP1EO and NP2EO and 0.05–0.2 μg/L for NPEC (Ahel, 1991). In addition to Croatia, different concentrations of the metabolites were also detected in Germany (0.002 μg/L NP in groundwater and 0.001 μg/L NP in drinking water), the US (0.077 μg/L NP1EO and 0.147 μg/L NP2EO) and Italy (0.061–0.12 μg/L NPEOs) during this time (Thiele et al., 1997).

Today, the concentrations of NP in groundwater range between 0.001 μg/L and 3.85 μg/L (Loos et al., 2010; Luo et al., 2014; Félix-Cañedo et al., 2013) due to landfill leachate, water from agricultural

Table 2
Exemplary analytical investigations of different biological matrices contaminated with APEO metabolites

compound	sample type	concentrations	column	detection	LOD	LOQ	reference
OP, OPEO, NP, NPEO	human adipose tissue	NP 19 - 85 ng/g lipids OP 0.58 - 4.07 ng/g lipids	glass capillary column coated with PS 086 (30 m × 0.3 mm, 0.2 μm)	GC-MS	NP: 20 pg/g (blood), NPxEO: 5ng/g (lipids), OPxEO: 0.5 ng/g (lipids)	-	Müller et al. 1998
NP	breast milk	0.3 ng/mL	Hypersil APS (125 × 4 mm i.d., 3 μm particle size)	HPLC-Fluorescence	9 ± 3 ng/g f.w.	27 ng/g f.w.	Günther et al. 2002
OP, NP	cord blood plasma	OP: up to 1.15 ng/mL NP: up to 15.17 ng/mL	DB-1 column (30 m x i.d. 0.32 mm, 0.25 μm)	GC-MS	-	NP & OP: 0.1 ng/mL	Tan et al. 2003
OP, NP	human blood	n.n.-15.17 ng/mL	DB-1 column (30 m, i. d. 0.32 mm x 0.25 μm)	GC-MS	-	NP & OP: 0.1 ng/mL	Tan & Mohd 2003
NP	seafood	46.6 - 197 μg/kg f.w.	DB-5 fused silica capillary column (30 m x 0.32 mm I.D., film thickness 0.25 μm)	GC-MS	14.6 ng/L (liquid-liquid-extraction); 0.164 ng/L (microwave assisted solvent extraction)	-	Basheer et al. 2004
OP, OPEO, NP	breast milk	OP 0.12 ng/mL OPEO 0.07 - 0.16ng/mL NP 32 ng/mL	DB-XLB column (30 m x 0.25 mm, 0.25 μm)	GC-MS	OP: 0.019 ng/mL; OP1EO: 0.036 ng/mL; OP2EO: 0.076 ng/mL; NP: 9.8 ng/mL; NP1EO: 45.1 ng/mL	OP: 0.023 ng/mL; OP1EO: 0.049 ng/mL; OP2EO: 0.112 ng/mL; NP: 12.1 ng/mL; NP1EO: 86.9 ng/mL	Ademello et al. 2008
OP, NP	adipose tissue of women	OP 4.5 ng/g NP 57 ng/g	ZB-5 MS Zebron capillary column (30 m 0.25 mm i.d.; 0.25 lm film thickness)	GC-MS	OP: 2.8 ng/g; NP: 10.5 ng/g	-	Lopez-Espinosa et al. 2009
OP, NP	breast milk	OP 1.29 ng/mL NP 4.47 ng/mL	DB-5MS capillary column (15 m x 0.25 mm i.d., 0.1 μm film)	GC-MS	OP: 0.01 ng/g; NP: 0.3 ng/g	OP: 0.2 ng/g; NP: 1.2 ng/g	Chen et al. 2010
NP, NPEO	roach bile	NP 6 - 13 μg/mL NP1EO 18 - 21 μg/mL NP2EO 75 - 135 μg/mL	HP5-MS fused silica capillary column (30 m × 0.25 mm i.d., 0.25 m film thickness)	GC-MS/MS	NP: 60.2 ng/mL; NP1EO: 11.0 ng/g; NP2EO: 327.0 ng/g	-	Fenlon et al. 2010
OP, NP	wild mussels & clams	OP n.d. - 6 μg/kg w/w NP 147 μg/kg w/w	unlisted	GC-MS	OP: 0.05 μg/kg w.w.; NP: 0.35 μg/kg w.w.	-	Bouzas et al. 2011
OP, NP	fish bile	OP 374 - 441 ng/g NP 4957 - 29218 ng/g	HP-5MS cross-linked 5% PH ME siloxane (30 m×0.25 mm i.d.)	GC-MS	not specified	-	Puy-Azumendi et al. 2013
OP, NP	human urine	OP 4.09 ng/mL NP 2.77 - 3.84 ng/mL	Agilent XDB-C18 (50 mm × 4.6 mm, 1.8 μm)	HPLC-MS/MS	OP & NP: 1.0 ng/mL	OP: 0.15 ng/mL NP: 0.18 ng/mL	Zhou et al. 2013
NP	lettuce and collards	1.18 - 926.9 μg/kg f.w.	Dionex Acclaim 120 C18 RP column (4.6 x 250 mm)	HPLC	not specified	-	Dodgen et al. 2013
NP	vegetables and fruits	<0.3 - 11 μg/kg f.w.	Rxi-5MS capillary column (30 m × 0.25 mm, 0.25 μm film thickness)	GC-MS/MS	OP: 0.1 μg/kg f.w.; NP: 0.3 μg/kg f.w.	OP: 0.3 μg/kg f.w.; NP: 1.0 μg/kg f.w.	Lu et al. 2013
OP, NP, NPEO	groundwater, pig blood	groundwater: OP 0.05 - 0.82 μg/L NP <0.025 - 0.043 μg/L NP1EO <0.025 - 2.27 μg/L NP2EO <0.025 - 0.69 μg/L pig blood: OP <0.5 - 566.32 μg/L NP 1.02 - 56.94 μg/L	XTerra RP18 column (4.6 × 250 mm × 5 μm, Waters) + Zorbax Eclipse XDB-C8 column (4.6 × 150 mm × 5 μm, Agilent, Santa Clara, CA, U.S. A.)	HPLC-Fluorescence	groundwater: all APEOs: 0.025 μg/L pig blood: OP: 0.5 μg/L; NP: 1.0 μg/L	- -	Chiu et al. 2014
NP, NPEO	mussels	NP 96 - 3000 ng/g d.w. NPEO 0 - 300 ng/g d. w.	Waters Xterra C18 column (100 mm x 2.1 mm i. d., 3.5 μm particle size)	LC-MS/MS	not specified	-	Dodder et al. 2014
OP	liver and intestine microsomes		Inertsil ODS-SP column (5 μm, 3.0 mm i.d. × 150 mm)	HPLC-Fluorescence	not specified	-	Hanioka et al. 2016
OP, NP	maternal blood & amniotic fluid	OP 5.46 ng/mL and 5.72 ng/mL NP 9.38 ng/mL and 8.44 ng/mL	HP-5MS capillary column (30 m, i. d. 0.25 mm x 0.25 μm)	GC-MS	OP: 0.63 ng/mL NP: 0.54 ng/mL	-	Shekhar et al. 2017
OP, NP	mussels	OP 0.8 - 176.1 ng/g d.w. NP n.d. - 263.8 ng/g d.w.	HYPERSIL GOLD C18 PAH column (250 x 4.6 mm; 5 μm)	HPLC-Fluorescence	-	OP: 0.8 ng/g d.w. NP: 1.0 ng/g d.w.	Staniszewska et al. 2017
NP	foodstuff	0.02 - 10.3 μg/kg	not specified	GC-MS	NP: 17 ng/g	NP: 27.5 ng/g	Günther et al. 2017
OP, NP	fish	OP n.d. - 1.78 ng/g w.w. NP n.d - 3.27 ng/g w.w.	HP-5MS capillary column (30 m × 0.25 mm i.d., 0.25 μm film)	GC-MS	OP: 0.18 ng/mL NP: 0.25 ng/mL	OP: 0.6 ng/mL NP: 0.82 ng/mL	Luo et al. 2017

land, or seepage from septic tanks and sewer systems (Luo et al., 2014). In India, OP concentrations of between LOQ (<10.9 ng/L) and 60 ng/L were detected in water from water treatment plants (Chen et al., 2013). Furthermore, OPs were detected in bottled water in Spain in the concentration range of 18.5 ng/L (Fabregat-Cabello et al., 2016). In contrast, NPs, OPs and their alkylphenol ethoxyacetic acids (AP1-2EC) were not detected (LOD = 20–100 ng/L) in treated water from a drinking water treatment plant in Barcelona (Petrovic et al., 2001). Bottled water from the Czech Republic showed a median OP concentration of 1.3 ng/L (Pernica et al., 2015). In a tropical urban catchment in Singapore, concentrations of other OPEO metabolites like octylphenol ethoxyacetic acid (OP1EC) and dicarboxylated alkylphenol ethoxyacetic acid were as high as 0.9 μg/L (Xu et al., 2011). The observed concentrations were determined during a specific time period; however, seasonal variations have to be taken into consideration (Motegi et al., 2007; Wu et al., 2013; Xu et al., 2006; Isobe et al., 2001; Gao et al., 2017). Enhanced degradation of NPE and OPE in warmer seasons occurs because of increased microbial activity (Li et al., 2004) and photolysis induced by sunlight (Ahel et al., 1994).

Depending on the ethoxylate chain length of the APEOs, they are considered to be either water insoluble and lipophilic (EO < 5) or water soluble and hydrophilic (EO > 5) (Ahel and Giger, 1993; Jonsson et al., 2008). Due to their very low partition coefficient, APEOs and their metabolites have the ability to bind with organic matter (Ying et al., 2002) and accumulate in animal tissue (Ahel and Giger, 1993; Ekelund et al., 1990), which allows them to enter the food chain.

Varying concentrations of NPs were found in different foods within the range of 0.1 and 100 μg/kg f.w. In drinking water, concentrations starting below the detection limit (<7.7 ng/L) were found, which went up to 0.3 μg/L in different countries. NP concentrations in various foodstuffs from supermarkets in Germany were first reported by Guenther et al. (2002) and ranged from 0.1 to 19.4 μg/kg f.w (Guenther et al., 2002). A comparable study was performed in Taiwan with commonly consumed foodstuffs, which showed the highest NP concentrations on oysters (235.8 ng/g) and salmon (123.8 ng/g) (Lu et al., 2007). In seafood, high concentrations of NPs were observed in Asia (Basheer et al., 2004; Isobe et al., 2007; Shao et al., 2007), Europe (Ferrara et al., 2005; Ferrara et al., 2008) and North America (Dodder et al., 2014). In various studies on vegetables and fruits in Sweden (Gyllenhammar et al., 2012), Spain (Cacho et al., 2012) and Florida (Lu et al., 2013), NP concentrations of between 5 and 50 μg/kg f.w. were observed. The highest quantities were detected in carrots, pumpkins, apples and citrus fruit. Accumulation studies of NP in roots, stems and leaves of lettuce and collards revealed a major difference between the variable parts of the plant ranging from 0.22 ng/g up to 927 ng/g (Dodgen et al., 2013). Loyo-Rosales et al. (2004) determined the concentrations of NP in different bottled waters with varying polymer materials and found them to be in the range of 15–300 ng/L (Loyo-Rosales et al., 2004). In other studies, concentrations of between <7.7 ng/L and 84 ng/L were detected in public fountains and bottled mineral water in Italy (Maggioni et al., 2013). In commercial soft drinks, concentrations similar to those in bottled mineral water were detected (Li et al., 2013). With the above-mentioned concentrations, Guenther et al. calculated a daily NP intake of 7.5 μg/day exists for adults, and for infants the range is from 0.2 to 1.4 μg/day depending on the food consumed. Other calculated daily intakes of NPs for adults varied between 0.067 and 0.37 μg/kg/day in foodstuffs (Lu et al., 2013; Shao et al., 2007; Ferrara et al., 2005; Ferrara et al., 2008; Gyllenhammar et al., 2012) and between 0.36 and 0.6 μg/kg in bottled drinking water (Loyo-Rosales et al., 2004). Another study by Raecker et al. (2011) calculated a daily NP intake in the range of 0.23–0.65 μg/kg bw/day for high consumers such as babies. In addition, OPs were identified in 80% of the food samples taken, which showed concentrations of up to 0.6 μg/kg (Raecker et al., 2011). If we look at the Gulf of Gdańsk, fish like herring, flounder and cod are considered safe food sources for human consumption with respect to their alkylphenol content (Staniszewska et al., 2014). A Taiwanese study calculated an average daily NP intake of 28.04 μg/day and an estimated intake of 31.4 μg/day, which suggests a 4-fold to 8.5-fold higher daily intake of NP in Taiwan than in Germany and New Zealand (Lu et al., 2007). In Italy, a maximum NP daily intake of 3.94 μg/kg/day was calculated, and for OP researchers found an intake that was at least six orders of magnitude lower than the no-observed-adverse-effect level (NOAEL) of 10 mg/kg/day (Ademollo et al., 2008). The information in this passage is collected in Table 2.

Comparing the measurement results of the past and today reveals a reduction of APEO metabolites as a consequence of voluntary disclosures and legislation in Europe.

4.2. Human tissues and blood

APEO metabolites are already found in several human tissues and blood. Concentrations of NP in blood samples of humans vary between below the detection limit and up to 53.21 ng/g (Tan and Mohd, 2003; Shekhar et al., 2017; Peters, 2003; Chen et al., 2005), whereas the concentrations of OP vary between below the detection limit and 16.02 ng/g (Chen et al., 2005). In an Indian population EDC's were investigated in maternal blood plasma and the NP and OP mean concentrations were 8.91 ng/mL and 5.59 ng/mL (Shekhar et al., 2017). Other human tissues where APEO metabolites are found include adipose tissues, liver, amniotic fluid, breast milk, urine and semen. In adipose tissue, the maximum NP concentration is 85 ng/g lipids and 4.07 ng/g lipids for OPs (Müller et al., 1998). Metabolites such as NP, OP and OPEO were measured in breast milk and found to be in a range of 0.07–32 ng/mL (Guenther et al., 2002; Ademollo et al., 2008; Chen et al., 2010; Otaka et al., 2003). Ademollo et al. found the highest concentration of NP in the breast milk of Italian woman (13–56 μg/L). However, their measured OP concentrations were at least one order of magnitude lower than those measured by Ye et al. (Ademollo et al., 2008; Ye et al., 2006). Due to the consumption of NP and OP-polluted foodstuffs, concentrations in the range of 5.4–23,829.5 ng/g dry weight and 5.6–481.5 ng/g dry weight were detected in the hair of Pomeranian inhabitants (Nehring et al., 2017a). An analysis of human urine samples revealed an NP concentration range of between 2.77 and 42.06 ng/mL (Zhou et al., 2013; Chen et al., 2005). In a Korean adult population study the mean urinary concentrations of 4-NP and 4-t-OP were 3.7 ng/mL and 0.6 ng/mL respectively (Park and Kim, 2017), whereas the concentrations in a Chinese study ranged between 1.69 and 27.8 ng/mL for NP, and between 0.407 and 11.1 ng/mL for OP (Xiao et al., 2011). In a US population study by Calafat et al., OP concentrations ranged between 1.6 and 3.2 ng/mL (Calafat et al., 2007).

4.3. Other biological matrices

The accumulation potential of APEO metabolites, especially in several aquatic species, has been confirmed in many studies (Staniszewska et al., 2017; Ekelund et al., 1990; Wenzel et al., 2004; Ahel et al., 1993; Giger et al., 1981). However, one study suggested that NP does not accumulate in tissue and that the half-life of NP in rainbow trout tissue is about 24–48 h (Arukwe et al., 1997). The concentrations of NP in mussels from Europe, South America and Asia are ranged between <10 ng/g d.w. and nearly 180 ng/g d.w. whereas the OP maximum concentrations is <40 ng/g d.w (Staniszewska et al., 2017). Another study at the Gulf of Gdansk measured NP and OP concentrations in phytoplankton, zooplankton, mussels and different fish spiecies with maximum concentration of 87.5 ng/g d.w. of OP in phytoplankton and 263.7 ng/g d.w. of NP in zooplankton (Staniszewska et al., 2014). The same group found that the OP and NP concentrations depended on anthropogenic factors and phytoplankton or zooplankton properties (Staniszewska et al., 2015; Staniszewska et al., 2016). Baltic grey seals placenta and fur and feathers of herring gulls are also biological matrices in which OP and NP have been detected (Nehring et al., 2017a; Nehring et al., 2017b). Other metabolites like the NP1EO and NP2EO have been

measured in mussels in the range of 6.3–300 ng/g d.w. and <LOQ–140 ng/g d.w (Dodder et al., 2014).

5. Toxicity

Given the key role that estrogens play in developmental processes and reproductive functions, compounds with an estrogenic effect (i.e. APEO metabolities) are a source of major concern (Bhatt et al., 1992; Guillette et al., 1994; Cooper and Kavlock, 1997; Akingbemi and Hardy, 2001). For NP and OP, it has been shown that they are acutely toxic to fish, invertebrates and algae at concentrations of 17–3000 μg/L and chronic toxicity has been shown in the range of 3.7–6 μg/L (Servos, 1999). An exemplary reference list is given in Table 3 regarding to the toxicity of APEO metabolites.

In addition to the already well-known estrogenic potential of APEO metabolites, another important issue is their impact on the developing and developed nervous and immune systems of mammals. In the next section, we start with a brief discussion of the estrogenic potential of APEO metabolites, followed by an overview of their effects on the nervous and immune systems and a brief examination of low-dose effects. Table 4 gives a brief overview of publications on the effects of EDCs on the nervous and immune system.

5.1. Estrogenic potential

The estrogenic potential of NP in mammals was accidently discovered by Soto et al. (Soto et al., 1991) and confirmed by different in vitro (gene expression (White, 1994; de Weert et al., 2008; ter Veld et al., 2008)), *E*-screen (Soto et al., 1995; Preuss et al., 2006), yeast screen (Kim et al., 2004; Routledge and Sumpter, 1996; Saito et al., 2007) and in vivo bioassay studies with rats (Sharpe and Skakkebaek, 1993; Lee, 1998; Nagao et al., 2000; Laws, 2000), zebrafish (Saputra and Yen, 2015), rainbow trout (Jobling et al., 1996), and Japanese medaka (Gray and Metcalfe, 1997). Besides NP, estrogenic activity in fish was also reported for OP, NP2EO, NP1EC and NP2EC (White, 1994; Routledge and Sumpter, 1996; Jobling et al., 1996; Tanghe et al., 1999; Sumpter and Jobling, 1995; Wolff et al., 2015). Estrogens have the potential to bind with the progesterone and estrogen receptors (ER) with subtypes ERα or ERβ, via the classical or membrane-bound ER, in a competitive manner with 17β-estradiol, and are able to transactivate both receptors in reporter assays (Sato et al., 2002; Kuiper et al., 1998; Amaro et al., 2014). The classical genomic pathway has several steps, which involve translocation of the ER into the cell nucleus, receptor dimerization, conformation change into an active complex, and binding to the estrogen receptor element (ERE), which leads to regulatory changes of the transcription (Pettersson et al., 1997; Fliss et al., 2000). Another typical cascade pathway for estrogens is the membrane-bound ER signaling pathway. The estrogen will first bind to a G protein-coupled receptor (GPR30) and activate the mitogen-activated protein kinase (MAPK), signaling pathway with several steps of phosphorylation, and end with the activation of nuclear transcription factors (Filardo et al., 2007). Diseases are often an occurrence of dysregulated MAPK, either directly or indirectly (Yang, 2015). A well-studied and interesting model for the study of estrogen-like activity is the human placenta, which is an estrogen target tissue expressing both ERα and ERβ (Bechi, 2006; Rama et al., 2004; Fujimoto et al., 2005). For further information, please refer to the literature.

With regard to alkylphenols, OP concentrations in the environment may be lower than those for NP (Blake and Ashiru, 1997). However, various in vitro experiments have shown greater estrogenic potential (White, 1994; Nagel et al., 1997) of OPs with estrogenic activity at concentrations of around 0.1 μM.

APECs are found in the environment at concentrations of up to 931 μg/L. However, even though the estrogenic potential of APECs is less than that of APs, they still contribute to the total estrogenic potential either individually or as a mixture (Chiu et al., 2010). In a risk assessment study of municipal effluents in Canada, an estimated total estrogenic potential was calculated. The findings showed that, if only the NP concentrations were taken, the estrogenic response would not exceed the threshold of 1 μg/L. However, if the response of NPEOs were added to the NP effect, approximately 15% of the sites would exceed the threshold, and that close to 60% would exceed the threshold if NPECs were considered (Bennie et al., 2001).

As nonylphenol is a very complex endocrine disruptor consisting of many isomers with varying estrogenic potentials (Gabriel et al., 2008; Kim et al., 2004; Kim et al., 2005; Uchiyama et al., 2008; Preuss et al., 2006), it is important to quantitate and identify the single isomers. For example until now, investigations of nonylphenol contamination in foodstuffs were restricted to bulk determinations of total NP concentrations. This procedure is no longer appropriate because recent investigations have shown that the isomer composition may differ depending on the individual foodstuff being studied (Günther et al., 2017). Sum parameters should no longer be admissible and an isomer-specific approach will be necessary for future investigations, not only in food science but in all other matrices as well.

5.2. Effect on nervous system and cognitive function

APEO metabolites are able to interact with the nervous system (Jie et al., 2013a; Couderc et al., 2014; Jie et al., 2016), to influence cognitive function (Mao et al., 2010; Kawaguchi et al., 2015a; Kawaguchi et al., 2015b; Kazemi et al., 2018; Jie et al., 2013b) and can also cause inflammation, cell damage or apoptosis. High concentrations of AP, and especially NP, were determined in fat tissue with a median of 259 nM (Lopez-Espinosa et al., 2009) and in plasma with 241 nM (Chen et al., 2005). However, there are no documented concentrations of NP in nerve tissue. In a study by Yokosuka et al. (2008), it was shown that NP has an impact on the development of dendritic and synaptic cells as well as on the differentiation of astrocytes (Yokosuka et al., 2008). Besides these findings, it was also confirmed that NP has effects similar to those of 17β-estradiol. Other studies with NP have shown enhanced damage of weakened cells or increased apoptosis of PC12 cells (Sato

Table 3
Exemplary register of toxicity of different APEO metabolites

compound	species	end point	concentration	reference
NP	bacteria (Azobacter sp.)	optical density after 72h	18.8 - 112.8 mg/kg	Martensson and Torstensson 1996
OP	bovine oocytes	24 h	0.0001 - 1 μg/mL	Pocar et al. 2003
NP	Invertebrate (Folsomia fimetaria)	EC_{50}, 21 days	5 - 133 mg/kg	Scott-Forsmand and Krogh 2004, Sorensen and Holmstrup 2005
	Invertebrate (Folsomia candid)	EC_{50}, 21 days	5 - 133 mg/kg	Scott-Forsmand and Krogh 2004, Sorensen and Holmstrup 2005
NPEs	Fish (Promelas, Pimephales)	LC_{50}, 96h	190 mg/L	TenEyck and Markee 2007
NPEs	Crustaceans (Arcatia tonsa)	LC_{50}, 48h	359 mg/L	Gonzalez et al. 2012, TenEyck and Markee 2007
$NP_{10}EO$	*Vibrio fischeri*	percent bioluminescence inhibition		Karci et al. 2013
NP	*Cyclotella caspia*	EC_{50}, 96h	0.18 mg/L	Liu et al. 2013
OP	zebrafish embryos	LD_{50}, 3 days	1.0 μM	Saputra et al. 2015
NP	*Gracilaria lemaneiformis*	increased percentage of tail DNA	0.2 - 1.0 mg/L	Zhong et al. 2017b

Table 4
Exemplary listing of different experiments studing the effect of APEO metabolites on nervous and immune system

compound	medium	dose	effect	reference
NP	rat striatum	1, 5 & 10 μM	hydroxy radical formation	Obata & Kubota 2000
NP	rat striatum	10 μM	hydroxy radical formation	Obata et al. 2001
OP & NP	PC12 cells	50, 100 & 500 μM	neurological and behavioral disturbances	Talorete et al. 2001
NP	F1 rats	0, 2, 16 & 60 mg/kg/day	no gross alteration in Morris water maze performance	Flynn et al. 2002
NP	organotypic hippocampal culture	1 pM - 100 μM	influence on synaptogenesis and neuronal vulnerability	Sato et al. 2002
NP	rat hippocampal and cortical neurons	10 nM & 10 μM	Inhibition of staurosporine-induced neuronal cell death	Negishi et al. 2003
NP	PC12 cells	< 100 ng/mL	enhanced apoptosis	Aoki et al. 2004
NP	murine neural stem cells	1, 3 & 10 μM	death of neural stem cells	Kudo et al. 2004
OP & NP	Purkinje cell in rats	OP:2 & 20 μg/μL NP:20μg/μL	OP: promotion of dendritic growth during neonatal life NP: no significant effect	Shikimi et al. 2004
NP	Xenopus & PC12 cells	5 μM	inhibition of protein kinase A activity	Bevan et al. 2006
OP & NP	human embyonic stem cell	12.5 - 200 μM	higher sensitivity to toxicants of hEs cell-derived neural progenitor cells	Kim et al. 2006
NP	neural cells of chicken embryo model	19 pg/mL	nervous system susceptible to damaging events	Pretorius et al. 2006
OP & NP	brain tissue of male rats	25 mg/kg/day	oxidative damage	Aydogan et al. 2008
NP	PC12 cells	0, 45 & 60 μM	ER stress-mediated apoptosis	Kusunoki et al. 2008
NP	mouse brain (*in situ*)	100 & 200 mg/kg/day	sensitisation to apoptosis	Mao et al. 2008
NP	hippocampal neurons	1 - 100 nM	Rapid modulation of synaptic plasticity	Ogiue-Ikeda et al. 2008
NP	fetal rat hypothalamic cells	10 & 100 nM & 1μM	affect development of fetal rat hypothalamic cells in vitro	Yokosuka et al. 2008
NP	mouse brain	0, 50, 100 & 200 mg/kg/day	potential to induce the chronic inflammation or cause neurotoxicity	Zhang et al. 2008
NP	hippocampal rat neurons	1 μM	inhibition of neurite outgrowth	Matsunaga et al. 2010
NP	mouse (*in situ*)	0, 50, 100 & 200 mg/kg/day	generation of oxidative stress and cognitive impairment in male mcie	Mao et al. 2011
NP	PC12 cells	25.6 μM	endoplasmic reticulum (ER) stress-associated apoptosis	Sasaya et al. 2012
NP	F1 rats	50 & 100 mg/kg/day	nervous development impairment	Jie et al. 2013
4-n-NP	F1 rats	0, 5 & 200 mg/kg/day	behavioral & neuro-developmental impairments	Couderc et al. 2014
NP	mouse embryonic neuronal cells	5 & 10 μM	impairment of ER- and stimulation of RXR-mediated signaling pathways	Litwa et al. 2014
NP	PC12 cells	0.1-100 nM	changes in the cellular machinery responsible for neuronal differentiation	Nishimura et al. 2014
NP	Sertoli cells	0.01, 0.1, 1 & 10 μM	disrupting structure and function of Sertoli cells in vitro and hormone levels in serum	Hu et al. 2014
NP	Sprague-Dawley rats	0.5 & 5 mg/kg/day	impairment of spatial learning & memory performance	Kawaguchi et al. 2015a
NP	male rat offspring	1 & 10 mg/kg/day	improvement of spatial learning & memory	Kawaguchi et al. 2015b
NP	F1 rats	25, 50 & 100 mg/kg/day	inhibition of neuronal development 6 differentation	Jie et al. 2016
NP	mouse hippocampal cells	5 & 10 μM	apoptotic and neurotoxic actions of nonylphenol	Litwa et al. 2016
OP & NP	JEG-3 human placental cells	36 - 40 μM	differential toxicity and ability to modulate placental aromatase activity	Pérez-Albaladejo et al. 2017
NP	human chorioonic gonadotropin	0.04, 0.2, 1.0, 2.5 & 5.0 μg/mL	able to influence hormonal profile, cell viability and generate ROS	Jambor et al. 2017

et al., 2002; Aoki et al., 2004). PC12 cells were also used to observe neuronal differentiation when exposed to NP and it was shown that the exposure could lead to an inhibition of the neuronal growth factor (Bevan et al., 2006; Nishimura et al., 2014). Changes of glial fibrillary acidic protein were found in the hippocampus of rat pups that were lactated by NP-exposed dams (Jie et al., 2016). Another animal study with rat Purkinje cells showed no effect of NP on Purkinje dendritic growth although NPs were injected into the cerebrospinal fluid. However, OP promotes a dose-dependent dendritic outgrowth of Purkinje cells without effect on soma or cell number (Shikimi et al., 2004). The exposure of murine neural stem cells to NP leads to inhibited cell growth in a concentration-dependent manner as well as nuclear condensation, DNA fragmentation and the activation of caspase 3 (Kudo et al., 2004). Agonistic effects were observed with NP in recombinant human microtubule-associated protein 2C (rhMAP2C) experiments with inhibiting MAP2-mediated neurite outgrowth, which could affect dendritic outgrowth in hippocampal neurons and lead to psychological disorders following chronic exposure during early neuronal development (Matsunaga et al., 2010). In an *in ovo* neural chick embryo model, it was shown that NP exposure leads to irregular cell surfaces with pseudopodia, cell shrinkage and breakage in the plasma membrane, which are typical signs of apoptosis (Pretorius et al., 2006). Different studies have confirmed a caspase 3 activation in neuronal cells leading to apoptosis (Kusunoki et al., 2008; Sasaya et al., 2012; Litwa et al., 2014; Mao et al., 2012). Another factor in the investigation of cell damage is to measure oxidative stress or inflammatory occurrence. The effect of NP exposure alone and combined with vitamin C was studied with rats (Aydoğan et al., 2008). The results of this study showed increased oxidative stress in rat brains.

Finally, the influence of EDCs could lead to a change in behaviour (Jie et al., 2013b). In laboratory animal studies of mated pairs, positive associations between NP exposure and harmful effects on nerve behavioral capacity and/or learning and memory capacity were reported (Flynn et al., 2002; Mao et al., 2010; Jie et al., 2010; Xia et al., 2010). Results by Xia et al. indicate that NP exposure could lead to inhibition of locomotor activity and aggressive behaviour of male zebrafish, and in addition may inhibit group preference of male and female zebrafish (*Danio rerio*) (Xia et al., 2010). Another study with Sprague-Dawley rats showed that NP exposure with up to 750 ppm had no effect on Morris water maze performance test with young, adult, or middle-aged ovariectomized rats (Flynn et al., 2002) but a low-dose exposure experiment of NP showed a slight impairment of spatial learning and memory performance with the same rat type (Kawaguchi et al., 2015a). Whereas the results by Mao et al. indicate that a dosage of 200 mg/kg/day NP decreases locomotion and exploration in mice (Mao et al., 2010). A recent regression analysis shows a significant linear correlation between NP concentration and behavioral impairment (Kazemi et al., 2018).

5.3. Effect on immune system

The immune system is a vulnerable system that can respond to changes with an allergic reaction. In recent decades, there has been an increase in allergic diseases. These complex diseases are strongly dependent on gene-environment interactions and epidemiological studies

have shown that a variety of risk factors are able to trigger allergic diseases. One of these risk factors is the endocrine-disrupting chemical (EDC) group, which can trigger or even exacerbate allergic diseases (Suen et al., 2012). Allergic signs are usually associated with high levels of serum immunoglobulin E (IgE) and allergen-specific IgE and eosinophilia (Lee et al., 2003; Coyle et al., 1996; Eum et al., 1995). Cytokines such as interleukin (IL) 4, IL-5 and IL-13 which are expressed by differentiated T cells are responsible for allergic diseases (Kuo et al., 2014). The increase in IgE and antigen-specific IgG_1 is observed for alkylphenols in serum of NC/Nga mice and an aggravation of atopic dermatitis-like skin lesions is induced by alkylphenols (Sadakane et al., 2014).

A recent review looks at the effect of EDCs on adipogenesis and osteogenesis in mesenchymal stem cells, which are triggered by the immune system (Bateman et al., 2017).

Because NP and OP possess low solubility, high hydrophobicity and low estrogenic activity, they are able to accumulate in the human body and trigger allergic diseases. Both NP and OP are able to influence T cells, which are important in the initiation and maintenance of asthma in mice by altering cytokine synthesis (Lee et al., 2003; Iwata et al., 2004; Lee et al., 2004). Another immunoregulatory cell type is the human dendritic cell, which may be influenced by NP and 4-OP (Hung et al., 2009). It has been shown that the immune response of lymphocytes and macrophages can be affected by NP (Lee et al., 2017b). However, based on a cDNA library of frog (*Rana chensinensis*), OP was able to induce an immune response as well as affecting multiple physiological processes (Li et al., 2016).

Most studies use high concentrations of alkylphenols for their experiments, which are unlikely to occur outside the laboratory, but a recent study showed that, for the human macrophage-like THP-1 cell, OP is able to trigger an immune response even at low concentrations (0.001 μM) (Couleau et al., 2015).

5.4. Low dose effects

In modern society, chemicals are a part of life and their use and release into the environment is continuously increasing. This includes EDCs and especially APEO metabolites. Even at low doses, EDCs can interfere with the endocrine and reproductive system and inhibit the synthesis and/or transport of specific hormones (Neubert, 1997; Kavlock and Ankley, 1996). In addition, hormones are a key factor in the proper development of various organ systems and tissues such as those of the reproductive tract, brain and neuroendocrine system (Kortenkamp et al., 2011). Complications in pregnancy such as implantation failure and loss of the fetus are some of the results of an unbalanced cytokine network at the maternal-fetal interface (Bechi et al., 2009). Endocrine disruptors like NPs raise considerable concerns about maternal exposure during pregnancy, even in low doses. In an in vitro experiment with chorionic villus explants (placental tissue), Bechi (2006) showed that the estrogen-like activity of NP is much higher in first-trimester human placenta than 17β-estradiol (Bechi, 2006). In a nanomolar concentration range, the effects of NP were an increase in trophoblast differentiation and cell apoptosis. Another study with Sertoli cells and serum reproductive hormones in prepubertal male rats, both in vitro and in vivo, showed that NP can disrupt the structure and function of Sertoli cells in vitro and hormone levels in serum even at low doses (Hu et al., 2014). A combination of NP and OP in environmentally relevant doses indicates that chronic exposure to this mixture modifies reproductive parameters in female mice (Patiño-García et al., 2018).

The daily intake of APEO metabolites may be by far under the studied ones, but due to synergistic effects (among themselves or with other EDCs) (Hu et al., 2012), cells will respond to these EDCs. However, without such a consideration, the risk assessment is not sufficient for these types of contaminant.

6. Regulation

Due to the accumulation potential, poor degradability and toxicity of these metabolites, APEOs have been mainly replaced by alcohol ethoxylates in most western countries (Loos et al., 2007). In 1986, a voluntary restriction was introduced in Germany and a ban in the use of surfactants in laundry detergents was imposed in Switzerland (Renner, 1997). This was followed by a voluntary ban of APEOs in household cleaning products in northern Europe (England, France, Germany and Scandinavian countries) in 1995 and a restriction on their use in industrial cleaning applications in 2000 (Renner, 1997). Directive 2003/53/EC amending for the 26th time Council Directive 76/769/EEC relating to restrictions on the marketing and use of certain dangerous substances and preparations (nonylphenol, nonylphenol ethoxylate and cement), was passed in 2003 which was initiated by findings that nonylphenol is ubiquitous in food in 2002 (Guenther et al., 2002). Since 2005, all EU member countries have had to implement the directive in national law. More specifically, the directive stipulates that NPs and NPEOs "may not be placed on the market or used as a substance or constituent of preparations in concentrations equal or higher than 0.1% by mass" and with that regulatory to most industrial applications like pesticide formulations, industrial cleaning, industrial textile production and metal working industry. Another directive in 2008 (2008/105/EC) was passed, which regulates the allowable concentrations of NP and OP in surface waters (Directive 2008/105/EC of the European parliament and of the council, the European parliament and the council of the European Union, 2008). In 2013 the European Chemicals Agency (ECHA) included NP on the candidate list of substances of very high concern for inclusion in Annex XIV (Authorisation List) of regulation 1907/2006/EC (REACH) and recently proposed that NP not be recommended for inclusion in Annex XIV in this round (ECHA, 2017). On the same candidate list OP and its ethoxylates are included for the same reasons as NP but even now there are still no restrictions on OP in the EU and Russia (COHIBA Guidance Document No. 7, 2011), and this in spite of the fact that OP and OPEO as well as NP and NPEO were included in the North Sea Action Plan in 1990 and in the OSPAR list of chemicals for priority action in 2000 (COHIBA Guidance Document No. 7, 2011; OSPAR, 2009). In 1999, the Canadian government put NP and its ethoxylates on the list of toxic substances of the Canadian Environmental Protection Act. Thereafter in 2002 the Canadian Council of Ministers of the Environment released quality guidelines for water, sediment and soil with regard to the environmental levels of NP for the protection of aquatic life (Canadian Council of Ministers of the Environment, 2002a; Canadian Council of Ministers of the Environment, 2002b; Canadian Council of Ministers of the Environment, 2002c). In 2012, the U.S. Environmental Protection Agency (EPA) released an alternatives assessment through its Safer Choice program, which identified eight classes of surfactants that are safer than NPEOs. Under the Safer Detergents Stewardship Initiative, the EPA implemented a voluntary phase-out of NPEOs in industrial laundry detergents, through which companies committed to ending their use in liquid detergents by 2013 and in powder detergents by 2014. In 2014, the EPA proposed a Significant New Use Rule, which provided the agency the opportunity to review and evaluate any intended new or resumed use of NPs and NPEOs. The public comment period for this proposal ended on January 2015 (EPA, 2014).

Regulatory information from Asia is difficult to obtain. However, in 2011 Chemical Watch reported that Greenpeace East Asia had issued a release which stated that China had added NP to its list of restricted substances (Chemical Watch, 2011). The Association of Southeast Asian Nations (ASEAN) is a union of ten member states (Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Viet Nam, Lao PDR, Myanmar and Cambodia), which are taking measures to harmonise national standards with international standards. This harmonisation includes a regulation of NPs and NPEOs similar to that

of the EU. As far as we know, there are no regulations for APEOs or APs in Africa.

Nevertheless, APEOs are still being used in substantial amounts in institutional and industrial applications because of their low production costs (Chiu et al., 2010; Ribeiro et al., 2015). There is therefore a need for further legislation and restriction of APEOs. So our goal should be the ban of APEOs in any industrial and institutional process or at least their replacement with non-hazardous substances.

7. Conclusion

The influence of exposure in-utero and in early life to EDCs must be taken seriously, especially given their mechanistic effects on the fetus, even in low doses. The ubiquitous occurrence in environmental matrices of APEO metabolites means there is still a significant amount of work to be done to assess the full effect of these chemicals on public health. In this review the analytical methods that are used to study APEO metabolites, their occurrences in different matrices, and their toxicology and regulation have been summarized. The toxicity indicates that APEO metabolites may influence the development of nervous and immune systems, but due to the lack of epidemiologic data the human evidence is incomplete. Because there are multiple sources of human exposure to APEO metabolites and because these substances persist in the environment there is a need to help identify potentially widespread population health risks.

The most widely used APEO is nonylphenol ethoxylate (NPEO), which accounts for 80 to 85% of all APEOs produced (United States Environmental Protection Agency, 2010). Thus, the APEO metabolites NP, NP1EC, NP2EC, NP1EO, and NP2EO are especially important. These five estrogen-active compound classes are in themselves complex mixtures of isomers (different-branched nonyl side chains) and enantiomers. The estrogenic potentials of each of these isomers (and enantiomers) seem to be very different. Consequently, to determine the potential toxicological impact of metabolites of APEOs in the environment, biomatrices and human beings, an isomer- and enantiomer-specific approach is absolutely necessary in the future.

With the issues summarized in this review, research on metabolites of alkylphenol ethoxylates deals with a more complex multicomponent problem than those research on polychlorinated dibenzodioxines or polychlorinated bipenyls.

List of abbreviations

AP	alkylphenol
APEO	alkylphenol ethoxylate
AP1EC	(4-alkylphenoxy)acetic acid
AP2EC	(4-alkylphenoxy)ethoxy acetic acid
AP1EO	4-alkylphenol monoethoxylate
AP2EO	4-alkylphenol diethoxylate
CE	capillary elektrophoresis
DP	dodecylphenol
DPEO	dodecylphenol ethoxylate
ECD	endocrine-disrupting chemical
ECHA	European Chemicals Agency
EPA	US Environmental Protection Agency
ER	estrogen receptor
ESB	Environmental Specimen Bank
EU	European Union
FTIR	Fourier transform infrared spectroscopy
GC	gas chromatography
GPR30	G protein coupled receptor
LC	liquid chromatography
MS	mass spectrometry
NMR	nuclear magnetic resonance spectroscopy
NP	4-nonylphenol
NP1EC	4-nonylphenoxy acetic acid
NP2EC	4-nonylphenoxy ethoxy acetic acid
NPEO	4-nonylphenol ethoxylate
NP1EO	4-nonylphenol monoethoxylate
NP2EO	4-nonylphenol diethoxylate
OP	4-*tert.*-octylphenol
OPEO	octylphenol ethoxylate
QMS	quadrupole mass spectrometer
QuEChERS	quick easy cheap effective rugged and safe
REACH	regulation 1907/2006/EC
SBSE	stir bar sorptive extraction
SPE	solid phase extraction
tNP	technical nonylphenol
TOF-MS	time-of-flight mass spectrometer
UPLC-MS/MS	ultra-performance liquid chromatography tandem mass Spectrometry

Compliance with ethical standards

Conflict of interest

The authors declare that there exist no conflicting interests which may bias this research.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Not applicable.

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